REMARKS

STATUS OF THE CLAIMS

Claims 1, 2, 4, 5, 7, 8, 10, 11, 13-15, 21-26, 31, 34, 35 and 38-48 are pending as shown in the paper filed August 9, 2006 and claims 34 and 48 are under consideration.

REJECTIONS WITHDRAWN

Applicants note with appreciation withdrawal of the rejections under 35 U.S.C. § 112, 2nd paragraph and of claim 48 under 35 U.S.C. § 102(b) as well as the rejection of claim 34 under 35 U.S.C. § 103(a) (based on Vegeto in view of McEwan and Bledsoe in view of Liu).

35 U.S.C. § 102

Claim 34 is newly rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 95/19431 (hereinafter "Barbas"). (Final Office Action, pages 7-8). It was alleged that claim 34 no longer requires that the first polypeptide bind to the second polypeptide in a manner modulatable by a ligand and, as such, Barbas's Zif(C7)6-Jun/Zif-268-Fos heterodimer (Example 12) anticipates pending claim 34. *Id.*

Claim 34 is directed to a complex comprising a heterodimer (first and second polypeptides, at least one of which is an engineered C2H2 zinc finger protein) and a ligand. The Zif(C7)6-Jun:Zif-268-Fos heterodimers disclosed by Barbas do not comprise a ligand. Rather, the dimerization domains of Jun and Fos interact directly to form the heterodimer.

Therefore, because Barbas does not teach or suggest a complex comprising a heterodimer and a ligand as set forth in claim 34, withdrawal of this rejection is in order.

35 U.S.C. § 103

Claim 48 was again rejected as allegedly obvious over WO 93/23431 (hereinafter "Vegeto"), as evidenced by McEwan *et al.* and Bledsoe *et al.* in light of Liu *et al.* (Final Office Action, pages 3-6). In support of the rejection, it was again stated that Vegeto discloses mutated steroid hormone receptors and their uses as a molecular switch for

regulating nucleic acid expression in mammals, and glucocorticoid receptors as starting material for making such mutant receptors. *Id.* It was maintained that the skilled artisan would have been motivated to combine Vegeto with Liu (who teaches design and construction of selective six-finger zinc finger proteins) because of the nature of the problem to be solved by Vegeto; *i.e.*, regulation of expression of a nucleic acid in mammals, and Liu's capability of designing a protein that will bind to a single site in a mammalian genome. *Id.*

In their previous response, Applicants argued that there is no motivation to combine Vegeto with Liu. In particular, Applicants argued that, contrary to the Office's statements, Vegeto did not provide any motivation to regulate endogenous genes inasmuch as all this reference discloses is regulation of exogenous genes. Applicants also noted that the hypothetical modification of Vegeto's mutant receptor by replacing its DNA-binding domain with Liu's zinc finger protein would generate a non-functional product:

> A fusion protein comprising a six-finger zinc finger binding domain (recognizing an 18-nucleotide target site) joined to a steroid receptor would have to bind to a 36-nucleotide sequence (consisting of a repeat of the 18-nucleotide target) in order to function as a dimer. The chance of such a specific sequence occurring in a mammalian genome is 1 in 4^{36} or approximately 5×10^{-21}. Alternatively, binding of a single steroid receptor/zinc finger fusion protein to an 18-nucleotide site would not function to regulate gene expression, since steroid receptors function as homodimers. Thus, the proposed modification of Vegeto's invention would render it non-functional.[1]

These arguments were rejected in the Final Office Action. In particular, it was alleged that the motivation to modify the references can derive from a skilled artisan perceiving "a benefit in modifying the products taught in the prior art so as to obtain a product having the properties of the claimed invention." *Id.* at page 5, citing *In re Sernaker* and *In re Fulton.*

[1] See, page 12 of Response filed August 9, 2006

However, Applicants again submit that a *prima facie* case of obviousness has not been established. An obviousness rejection cannot be predicated on an unsupported allegation that a skilled artisan would somehow "perceive" the benefit of making the modification to the references. Rather, the test for determining obviousness is whether or not the desirability of the claimed subject matter is suggested by the references or art as a whole. A high level of skill in the art cannot be the basis of an obviousness rejection:

> "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).[2]

It is not enough that the references could be modified to arrive at the claimed subject matter, there must be reasons given in the reference(s) or the art suggesting the desirability of the particular combination:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (Claims were directed to an apparatus for producing an aerated cementitious composition by drawing air into the cementitious composition by driving the output pump at a capacity greater than the feed rate. The prior art reference taught that the feed means can be run at a variable speed, however the court found that this does not require that the output pump be run at the claimed speed so that air is drawn into the mixing chamber and is entrained in the ingredients during operation. Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.). See also *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992) (flexible landscape edging device which is conformable to a ground

[2] MPEP § 2143.01(I)

> surface of varying slope not suggested by combination of prior art references).[3]

Nor can a *prima facie* case of obviousness be based on the allegation that the proposed modification is within the capabilities of the skilled artisan:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) (Court reversed obviousness rejection involving technologically simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have motivated the skilled artisan to make the claimed invention); *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (The level of skill in the art cannot be relied upon to provide the suggestion to combine references.).[4]

In addition, if the proposed modification would render the reference's product (or method) as unsatisfactory for its intended purpose or change its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)[5]

Applying this law to the instant case, it is clear that it is not enough that Vegeto teaches molecular switches generally or that Liu teaches engineered C2H2 zinc finger proteins generally. The Office has not pointed to anything in either reference or the art as a whole that would motivate the skilled artisan to modify Vegeto's steroid receptor-containing, single DNA-binding domain, exogenous gene-regulating system to arrive at

[3] MPEP § 2143.01(III)
[4] MPEP §2143.01 (IV)
[5] MPEP § 2143.01 (V) and (VI)

the subject matter of claim 48, namely a two DNA-binding polypeptide system in which binding of the two polypeptides is modulated by a ligand.

To reiterate, in Vegeto's systems, there is a single DNA binding domain – either a natural steroid receptor DNA biding domain attached to a modified ligand binding domain (page 16, line 6-7 of Vegeto) or, alternatively, a fusion of a steroid receptor with a DNA binding domain in which the DNA-binding domain of the steroid receptor is replaced with "a DNA binding domain selected from the group consisting of GAL-4 binding domain, virus DNA binding site, insect DNA binding site or a non-mammalian DNA binding site." (page 16, lines 14-18 of Vegeto). Thus, there is nothing in Vegeto that suggests the desirability of systems (switches) comprising two DNA-binding polypeptide components whose interaction is modulated by a ligand, as set forth in claim 48.

For its part, Liu (or the art as a whole) does not contain any suggestion of switches comprising two DNA binding domains, at least one of which is an engineered C_2H_2 ZFP. Accordingly, the obviousness rejection cannot stand because the alleged motivation to combine is not reasonably supported by the teachings of the references or art as a whole.[6]

In addition to lack of motivation to modify, the Office has not established that there is a combination of Vegeto and Liu that would result in the claimed polypeptides. As noted above, Liu in no way teaches two DNA-binding polypeptides, where dimerization is mediated by a ligand. For its part, Vegeto is clear that the molecular switch includes either a steroid receptor DNA binding domain or a modified steroid receptor in which the native DNA binding domain is replaced. Thus, modifying Vegeto to include a ZFP as described in Liu would still not result in a system having two DNA-binding polypeptides whose binding is modulatable by a ligand. Furthermore, as previously noted, the hypothetical modifications would render Vegeto unsatisfactory for

[6] The instant case is therefore unlike in the cases cited in the Final Office Action (*Sernaker* and *Fulton*) because the Office has not adequately supported the contention that there was a recognition from the references or "drawn from a convincing line of reasoning based on established scientific principles" that some advantage would have resulted from the hypothetical modifications.

its intended purpose of using a molecular switch made up of a single DNA-binding domain to bind to an exogenous sequence.

It is only with Applicants' disclosure in hand that a skilled artisan would have made the combination of Vegeto and Liu set forth by the Examiner. *See In re Kotzab* 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) and *Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious." Accordingly, the rejection is an impermissible hindsight reconstruction of the claimed methods.

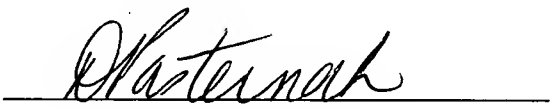
For all of the aforementioned reasons, Applicants again submit that the Office has failed to make a *prima facie* case of obviousness and, therefore, the rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance and request early notification to that effect. If the Examiner has any further issues or wishes to discuss any of the foregoing, he is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date: January 30, 2007

By: 

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